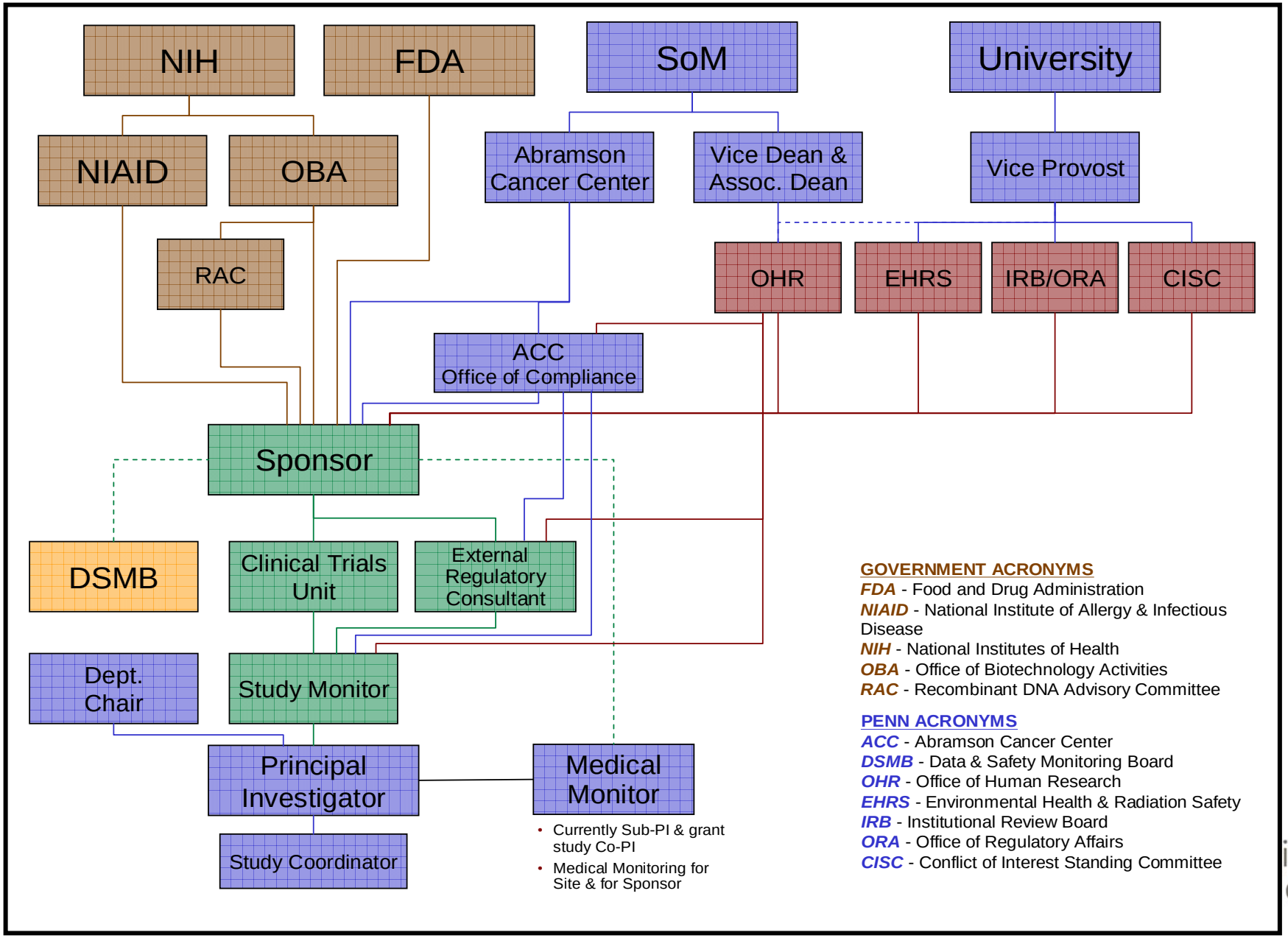
An Investigator's Perspective: How to Prepare for RAC Review

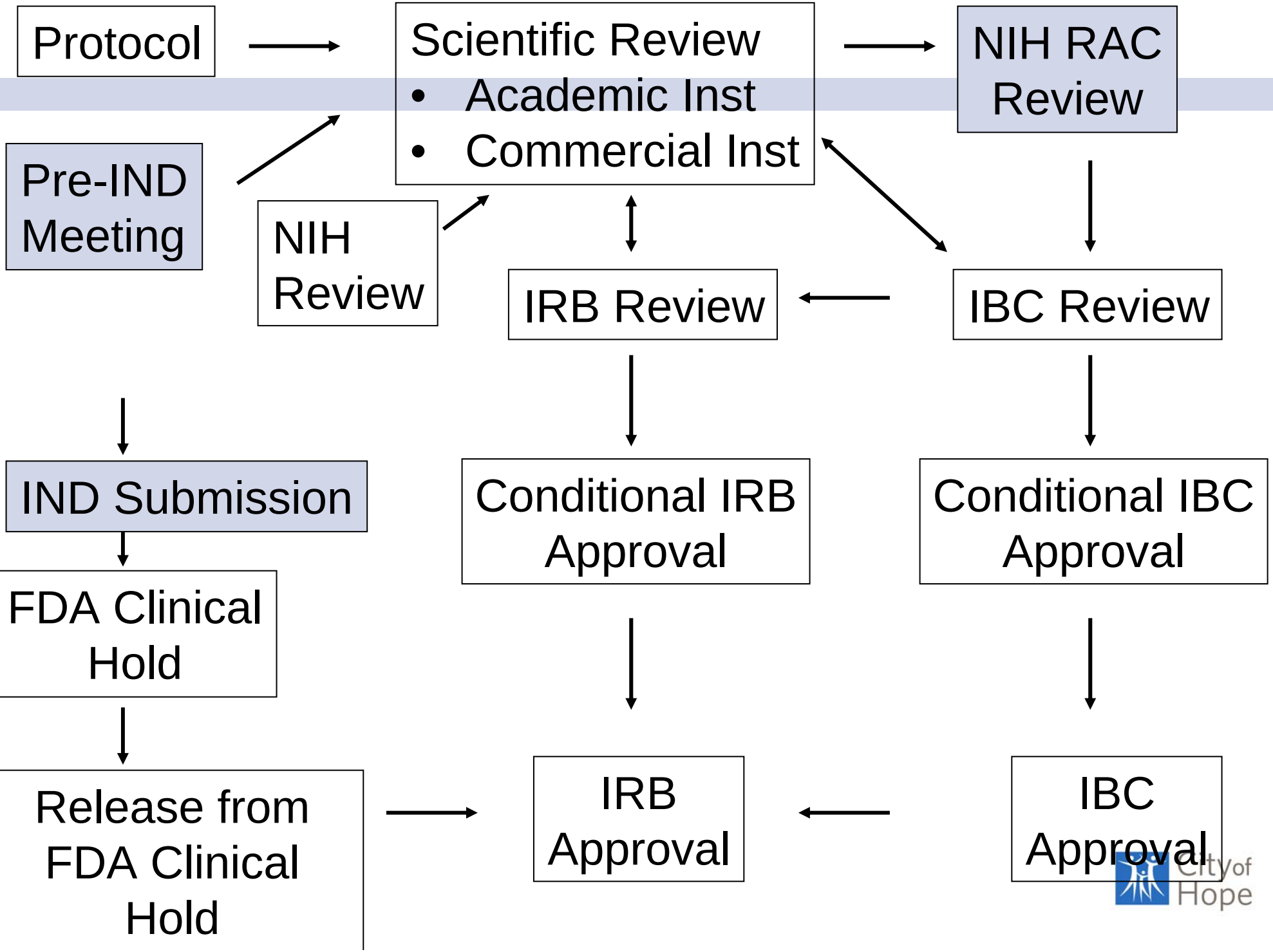
John A. Zaia, MD

May 30, 2007

Regulatory Oversight for Physician Sponsored IND

From Carl June




Protocol
Scientific Review
• Academic Inst
• Commercial Inst
NIH RAC Review
Pre-IND Meeting
NIH Review
IRB Review
IBC Review
IND Submission
Conditional IRB Approval
Conditional IBC Approval
FDA Clinical Hold
Release from FDA Clinical Hold
IRB Approval
IBC Approval

General Approach

- **Schedule: If you have not had a pre-IND meeting, plan to send the RAC submission at the same time that you send the request for an pre-IND meeting with FDA**

- **Preparation: Develop a working team that meets regularly to review the response to Appendix M**

- **Response to concerns: Return a RESPONSE TO CONCERNS to the RAC within 2 weeks after receiving the RAC concerns**

- **Preparation for the meeting: know the facts and address**

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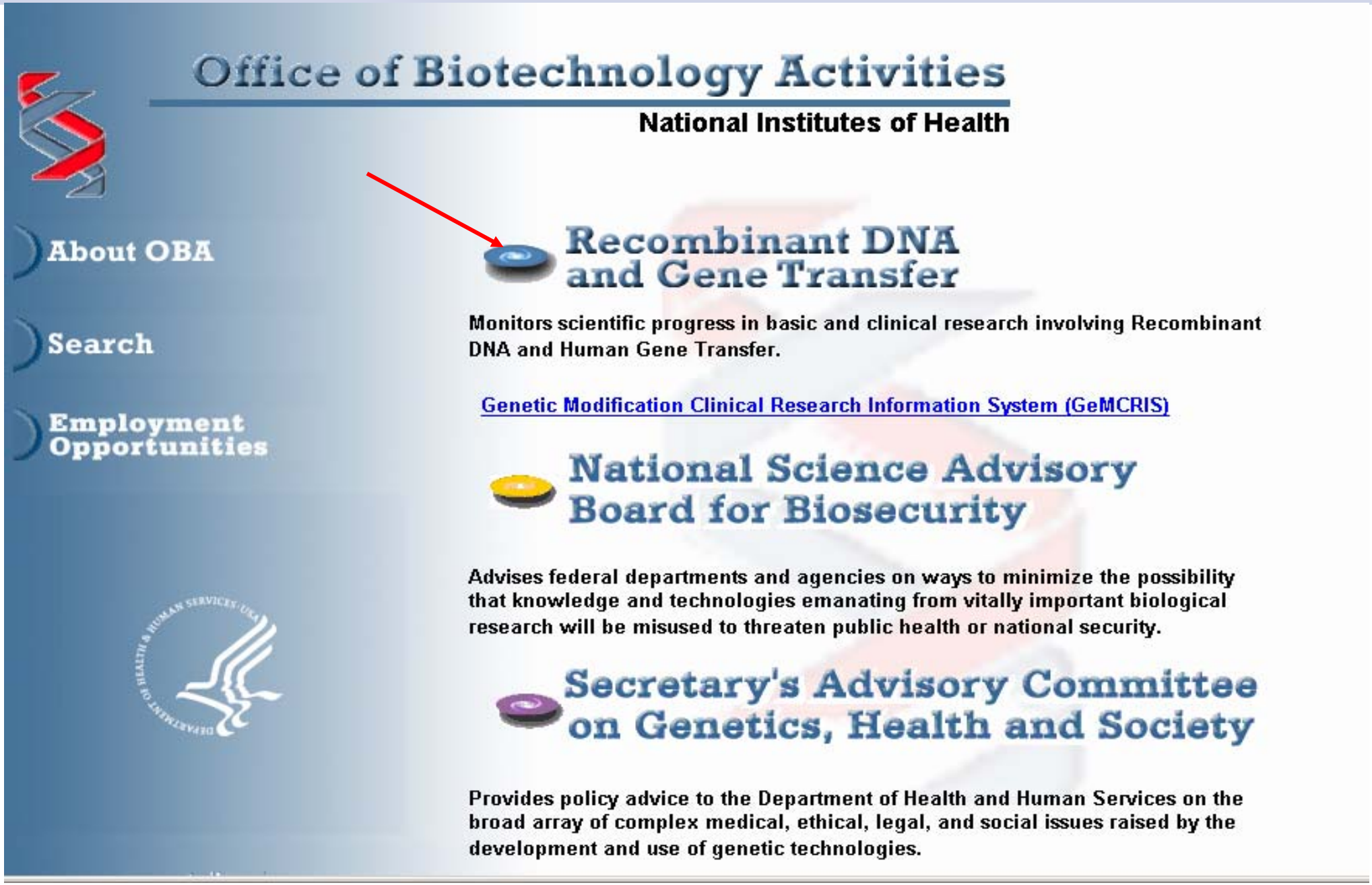

Recombinant DNA and Gene Transfer

Office of Biotechnology Activities

NSABB

GeMCRIS

SACGHS

SACX

OBA Home

- Latest News
- *NIH Guidelines for Research Involving Recombinant DNA Molecules*
- Compliance Reminder
- Database on Human Gene Transfer Trials (GeMCRIS)
- Informed Consent in Gene Transfer Research
- Recombinant DNA Advisory Committee
  - Frequently Asked Questions (FAQs) Regarding Protocol Submission and RAC Review
  - RAC Roster (as of 05/08/2007)
  - Meetings and Conferences
  - Protocol List and Other Documents
  - Serious Adverse Event Reporting Template
- Institutional Biosafety Committees

Page Updated : 05/08/2007/

Check Meeting Schedule

Meetings and Conferences

Recombinant DNA and Gene Transfer

- Latest News
- About RAC
- NIH Guidelines
- Documents
- GeMCRIS
- OBA Home

Future Meeting Dates and Protocol Submission Deadlines for Public Recombinant DNA Advisory Committee (RAC) Review*

PLEASE NOTE---MEETING DATES AND CONFERENCE ROOMS CHANGE PERIODICALLY

2007

- June 19-21, 2007, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 10, Bethesda, MD
  - 4/24/2007 -- Deadline for Protocol Submission
- September 17-19, 2007, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 10, Bethesda, MD
  - 7/23/2007 -- Deadline for Protocol Submission
- December 3-5, 2007, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 10, Bethesda, MD
  - 10/9/2007 -- Deadline for Protocol Submission

2008

- March 11-13, 2008, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 6, Bethesda, MD
- June 17-19, 2008, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 6, Bethesda, MD
- September 9-11, 2008, RAC -- NIH Main Campus, Natcher, Rm. E1&E2, Bethesda, MD
- December 9-11, 2008, RAC -- NIH Main Campus, Natcher, Rm. E1&E2, Bethesda, MD

Check Guidance Documents

Meetings and Conferences

Recombinant DNA and Gene Transfer

- Latest News
- About RAC
- NIH Guidelines
- Documents
- GeMCRIS
- OBA Home

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Documents

Recombinant DNA and Gene Transfer

NIH Guidelines

- NIH Guidelines

Recombinant DNA Advisory Committee -- RAC

- Serious Adverse Event Reporting Template
- Federal Registers
- Protocol List *(Tagged PDF)*
- Data Management Report
- RAC Roster
- RAC Charter (updated April 2005)
- Environmental Assessment and Finding of No Significant Impact, *approved by the NIH Director on October 22, 1997*

Documents of Interest

- Biosafety Considerations for Research with Lentiviral Vectors
- Conclusions and Recommendations of the RAC Gene Transfer Safety Symposium: Current Perspectives on Gene Transfer for X-SCID (March 15, 2005)
- Letter to Principal Investigators Conveying RAC Recommendations Regarding Adverse Events in a Gene Transfer Trial Studying X-linked SCID (March 20, 2003)
- Assessment of Adenoviral Vector Safety and Toxicity: Report of the

Documents of Interest

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- Assessment of Adenoviral Vector Safety and Toxicity: Report of the National Institutes of Health Recombinant DNA Advisory Committee
- Report from the ACD Working Group - Enhancing the Protection of Human Subjects in Gene Transfer Research at the National Institutes of Health, July 12, 2000.
- Statement by Dr. Amy Patterson to the Subcommittee on Public Health, U.S. Senate (PDF) (February 2, 2000)
- Letter from OBA--Requirements for Reporting Serious Adverse Events: Request for Institutional Review, (November 22, 1999) (PDF)
- FDA Letter to IND Sponsors/Principal Investigators of Gene Transfer Clinical Trials Regarding Protocol Submission and Adverse Event Requirements (November 5, 1999). (PDF)
- RAC Statement Regarding In Utero Gene Transfer Research (March 11, 1999).
- Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene (Orkin/Motulsky Report), (December 7, 1995)
- Ad Hoc Review Committee - Executive Summary of Findings and Recommendations (Verma Report), (September 8, 1995)
- Gene Therapy for Human Patients - Information for the General Public (April 1990)

Project-related Approa

Lentivirus T Cell Immunotherapy

AAV-based Rx of Hemophilia

Lentivirus Stem Cell Therapy

- **Understand the important iss**
  - Is this a first-in-human study?
  - Has this vector been used before?
  - Is the delivery system novel?

- **Plan your approach based on whether the main issues are expected to be vector related, transgene related, or protocol/patient related**

- **Assign each question from the Appendix M to a team member and discuss/finalize the response at a scheduled team meeting**

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Vector-Related Approach

- Emphasis will be on what is known about the vector.
- Full history of how it was constructed
- Sequence of the plasmids from which the vector is derived
- If the vector is not novel, and has been used in other studies, it will not be a significant concern unless those other studies were 'problematic'
- What is known about the vector in the cell system proposed?
- How does this vector help you reach the objectives of the proposed research?
- What is the evidence for replication non-competency?
- Explain the major safety concerns and how these will be approached

Transgene-Related Approach

- Emphasis will be on what is known about the transgene and why this choice of gene transfer is most appropriate
  - Full history of how it was derived; full DNA sequence
  - What are its regulatory elements? Copies per cell?
- Describe the "preparation, structure, composition" of the materials used to treat the cells or patient
- Results to demonstrate safety, efficacy, and feasibility
- Efficiency and duration of expression; integration of gene? rearrangement of transgene? Minimal expression needed for effect? Cell/Animal models of rx effect? Cell biology of transgene expression?

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Protocol/Patient Related Issues

- Why is this disease selected for experimental treatment?
- Natl history of this disease and objective measures of rx?
- Do alternative therapies exist? Pros and Cons of proposed rx?
- How will the gene transfer be delivered relative to the site of disease?
- How will the effects of the rx be monitored and correlated to transgene expression?
- Potential harmful effects? Minimalization of pathogenicity?
- Could the transgene be inadvertently delivered to germ cells? Sensitivity of the assay for transgene?

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Informed Consent

- Submit the consent that you intend to send to the IRB
- Use the readability indices in WORD to tone-down the verbiage
- Consider guidance documents
- Develop a consenting procedure that involves a third party
- Anticipate significant suggestions from the RAC
- Let your IRB review these suggestions and decide on how the consenting procedure and forms should read

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http://www4.od.nih.gov/oba/rac/ic/

National Institutes of Health
Office of Biotechnology Activities

NIH Guidance on Informed Consent For Gene Transfer Research

Print

- Introduction to Guidance
- Communication about the Study to Potential Participants
- ▼ Special Considerations for Informed Consent
- Consent Form
- ▼ General Requirements of Human Subjects Research
- ▼ Specific Requirements of Gene Transfer Research
- Additional Resources

Search Site

Introduction to Guidance

NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"

DISCUSSION

Since before the first clinical gene transfer trial began enrolling subjects, the National Institutes of Health (NIH) and its Recombinant DNA Advisory Committee (RAC) have sought to assist investigators in developing good consent forms and processes for clinical gene transfer research. Appendix M sections M-III and M-IV were added to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) to address points and issues related to informed consent that would benefit from particular attention. These sections address issues unique to gene transfer, as well as issues that gene transfer has in common with other forms of clinical research.

The requirements of Appendix M were always intended to be complementary to and are consistent with other requirements, regulations, and guidance documents, including 45 CFR 46, 21 CFR 50, and 21 CFR 56, and other guidance from the Office for Human Research Protections and the Food and Drug Administration. However, even after the promulgation of Appendix M-III and M-IV, NIH has continued to seek ways to assist investigators and others involved in the consent process for gene transfer trials.

In 2002, the NIH Office of Biotechnology Activities (NIH OBA) formed a RAC Informed Consent Working Group - composed of members of the RAC, outside

IMPORTANT NOTE

This guidance document DOES NOT constitute policy, requirements, rules, regulations, or laws enforced by NIH OBA or any other component of the Federal government. It is NOT a part of the NIH Guidelines for Research Involving Recombinant DNA Molecules, nor does it amend Appendix M. Instead, it provides supplementary material that may assist investigators and others in applying relevant sections of Appendix M, but its contents are neither prescribed nor required.

All sample consent form language provided in the guidance has been made "generic" and is meant only to illustrate how various issues could be conveyed; the samples are not endorsed by the above entities, are not intended to stand in for complete sections of a gene transfer research consent form, and should not necessarily be used verbatim. It is important to make informed consent language specific to each study design, population, and purpose, as well as to

Readability Index

- In WORD, use the  icon to determine the reading level
- Example:

  If you agree to participate in this study, you will undergo the following screening tests and procedures to make sure that you are eligible to receive the study drug: physical examination, x-rays, CT scans (an x-ray transmitted onto a computer that provides pictures of the inside of your body), urine test, blood tests requiring about 4 teaspoons of blood, electrocardiogram (EKG, test of your heart rhythm) and echocardiogram (use of high frequency sound waves to monitor the heart). If you are a woman of childbearing potential, you will also have a serum pregnancy test. If the screening evaluation shows that you are not eligible to receive study treatment, you will be taken off study and alternatives will be discussed.

  Flesch Reading Ease 40.2; Flesch-Kincaid Grade Level 12.0

  [Reader's Digest = 75; Havard Law Rev = 30]

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Readability Index

If you agree to this study, tests will be done to make sure that you can have this treatment. These are a physical exam, x-rays, CT scans (x-rays and computer pictures of the inside of your body), urine test, blood tests using about 4 teaspoons of blood, EKG and ECHO(tests of your heart rhythm and size). For those able to have children, a pregnancy test is done. If these tests show that you are not eligible for the study, other treatment is then discussed.

Flesch Reading Ease 73.7; Flesch-Kincaid Grade Level 8.2

The Flesch index shows whether the writing is difficult to read. It is based on the number of syllables per word and words per sentence. It was invented by Rudolph Flesch..

$$206.835 - 1.015\left(\frac{\text{total words}}{\text{total sentences}}\right) - 84.6\left(\frac{\text{total syllables}}{\text{total words}}\right)$$

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Response to RAC Concerns

- Anticipate a list of concerns from 2-4 reviewers assigned the protocol application
- Prepare a response to each concern
- This will become a document that is available to the RAC and to the public at this meeting

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Preparation for the RAC Meeting

- It is likely that more than one person will need to be prepared to address questions: the vectorologist, the cell biologist, and the clinician. But one person should be the main presenter.
- Make sure these persons are available by notifying them weeks in advance
- Anticipate a preparatory speaker if this is a novel use of gene transfer, e.g. siRNA
- Use the concerns of the reviewers to guide your presentation, I.e., do not waste your time on non-issues

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Summary

- Decide which issues are going to be important and focus on these: VECTOR, TRANSGENE, PROTOCOL
- Be efficient in preparing the documents by developing a systematic approach to covering the questions posed in the RAC Appendix M
- Follow the on-line requirements and guidances
- In general, submit your proposal to the RAC when you are ready for your pre-IND meeting and before your IRB/IBC submissions

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